II. REMARKS

Preliminary Remarks

In paragraph one of the official action, the examiner asserts the oath or declaration is defective because non-initialed and/or non-dated alterations have been made to the oath or declaration. The applicants will execute a new oath in compliance with 37 C.F.R. § 1.67(a) identifying this application by application number and filing date as required and will be filed under separate cover.

In paragraph 2, the examiner stated this application does not contain an abstract as required by 37 C.F.R. § 1.72(b). The applicants have submitted an abstract as set forth above.

In paragraph 3 of the official action, the examiner asserted several informalities. Specifically, the examiner requested that Brief Description of Drawings contain a specific reference to Figures 5A-H. The applicants have submitted specific references to Figures 5A-H. Support for these descriptions is found throughout the specification as originally filed, for example, on page 44, lines 1-16 in Example 4. In addition, the examiner alleges the specification and claims' reference to GenBank Accession Numbers is improper because the nucleic acid sequences and amino acid sequence in this database are subject to change overtime. Amendments removing recitation of GenBank Accession Numbers in the specification, and the cancellation of claim 4 obviate this objection. Finally, the examiner objected to the title as not being descriptive and suggested a new title from which the applicants have adopted and are grateful for the suggestion.

In paragraph 4 of the official action, the examiner requested that the remaining claims with language directed to the non-elected nucleic acid sequences set forth in SEQ ID NO: 1, 3, 4, or 5 be deleted. The cancellation of claims 3, 10, 34, and 35 obviate this objection.

New claim 41 is directed to an isolated nucleic acid comprising a nucleotide sequence selected from the group consisting of (a) the nucleotide sequence as set forth in SEQ ID NO:

2; (b) a nucleotide sequence encoding the polypeptide as set forth in SEQ ID NO: 7; and (c) a nucleotide sequence complimentary to (a) or (b). Support for the cited nucleic acids can be found throughout the specification, for example, on page 12, line 32 to page 13, line 15; page 17, lines 6-10, and Example 3.

Amended claim 10 is directed to a vector comprising the nucleic acid of claim 41. The applicants submit that the amended claim more succinctly defines the applicants' invention without narrowing the scope of the claim. Support for amended claim 10 is found in originally filed claim 10 and is not in response to any rejection.

Claims 11-14 have been amended to remove the phrase "recombinant DNA construct according to," an amendment which is not narrowing and which is not related to patentability. Support for these amendments can be found in the originally filed claims 11-14 and claim 10, from which claims 11-14 depend.

Amended claims 15 is directed to a host cell of claim 14 that is a prokaryotic cell while amended claim 16 is directed to a host cell of claim 14 that is a eukaryotic cell. The amendment to these claims helps define the subject matter of the claims more succinctly without narrowing the scope of the claim.

New claim 42 is directed to an isolated nucleic acid comprising a nucleic acid sequence that is at least 90% identical to the sequence of the nucleic acid sequence of claim 41 and encodes a polypeptide that is capable of binding a peripheral-type benzodiazepine receptor (PBR). Support for the phrases "at least 90% identical" and "capable of binding peripheral-type benzodiazepine receptor (PBR)" are found throughout the specification, for example, on page 18, lines 15-27 and Example 1.

New claim 43 is directed to an isolated nucleic acid comprising a nucleic acid sequence that is at least 90% identical to the sequence of the nucleic acid sequence of claim 41 and encodes a polypeptide that is capable of regulating steroid biosynthesis. Support for

the phrase "capable of regulating steroid biosynthesis" is found throughout the specification as originally filed, e.g., on page 42, lines 10-21 and page 51, lines 3-26.

New claim 44 is directed to an isolated nucleic acid comprising a nucleic acid sequence that is at least 90% identical to the sequence of the nucleic acid sequence of claim 41 and encodes a polypeptide that is capable mediating cholesterol delivery. Support for the phrase "capable of mediating cholesterol delivery" is found throughout the specification as originally filed, e.g., on page 51, lines 10-35.

New claim 45 is directed to an isolated nucleic acid that encodes a polypeptide that is capable of binding a peripheral-type benzodiazepine receptor (PBR) and hybridizes to the complement of the nucleic acid of claim 41 under the following stringent conditions: a final wash in 0.1X SSC at 65°C. Support for the stringent hybridization conditions is found on page 17, lines 11-18 of the specification. Support for the phrase "capable of binding peripheral-type benzodiazepine receptor (PBR)" and the highly stringent hybridization conditions at 65°C are found throughout the specification, e.g., page 17, lines 6-18, Example 1 and page 51, lines 27-31.

New claim 46 is directed to an isolated nucleic acid that encodes a polypeptide that is capable of regulating steroid biosynthesis and hybridizes to the complement of the nucleic acid of claim 41 under the following stringent conditions: a final wash in 0.1X SSC at 65°C. Support for the phrase "capable of regulating steroid biosynthesis" can be found throughout the specification as originally filed e.g., on page 42, lines 10-21 and page 51, lines 3-26.

New claim 47 is directed to an isolated nucleic acid that encodes a polypeptide that is capable of mediating cholesterol delivery and hybridizes to the complement of the nucleic acid of claim 41 under the following stringent conditions: a final wash in 0.1X SSC at 65°C. Support for the phrase "capable of mediating cholesterol delivery" can be found, for example, on page 51, lines 10-35 of the specification.

New claims 53-56 are directed to the nucleic acids of claim 42 in vectors, host cells, the process for producing peripheral-type benzodiazepine-receptor-associated protein-7 (PAP-7), and diagnostic reagents. Similarly, new claims 57-60 are directed to the nucleic acids of claim 43 in vectors, host cells, the process for producing PAP-7 and diagnostic reagents. New claims 61-64 are directed to the nucleic acids of claim 44 in vectors, host cells, the process for producing peripheral-type benzodiazepine-receptor-associated protein-7 (PAP-7), and diagnostic reagents. New claims 65-68 are directed to the nucleic acids of claim 45 in vectors, host cells, the process for producing peripheral-type benzodiazepine-receptor-associated protein-7 (PAP-7), and diagnostic reagents. New claims 69-73 are directed to the nucleic acids of claim 46 in vectors, host cells, the process for producing peripheral-type benzodiazepine-receptor-associated protein-7 (PAP-7), and diagnostic reagents. Finally, new claims 74-77 are directed to the nucleic acids of claim 47 in vectors, host cells, the process for producing peripheral-type benzodiazepine-receptor-associated protein-7 (PAP-7), and diagnostic reagents. Support for these new claims can be found, for example, original claims 11 and 14, page 18, line 28 to page 21, line 11, and page 26, line 23 to page 27, line 4.

Claims 6-8, 18-33, and 36-40 were canceled because these claims were withdrawn from consideration as being drawn to a non-elected invention, and not for any reason related to patentability.

The applicants do not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

Patentability Remarks

Rejection Pursuant to 35 U.S.C. §112, first paragraph, enablement–

The examiner rejected claims 1-5, 9-17, 34, and 35 pursuant to 35 U.S.C. § 112, first paragraph, for lack of enablement. In particular, the examiner asserted that while the specification was enabling for an isolated peripheral-type benzodiazepine receptor (PBR)-associated protein 7 (PAP-7) DNA sequence of SEQ ID NO:2 or for an isolated DNA sequence that encodes the PAP-7 amino acid sequence of SEQ ID NO:7, does not reasonably provide enablement for an isolated PBR-associated protein (PAP) DNA fragment or any portion thereof. The examiner further alleges the specification is not enabling for an isolated and purified DNA fragment which encodes a PBR-associated protein. The examiner still further alleges that the specification is also not enabling for any DNA fragments of SEQ ID NO:2 comprising at least 30 nucleotides or an isolated DNA fragment which encodes a peptide of PBR-associated protein, said DNA comprising a sequence specified in Genbank Accession Nos. AF022770 or AF020338 or a fragment of said sequence comprising at least 30 nucleotides. In addition, the examiner alleges that the specification is not enabling for an isolated PAP-7 DNA fragment or natural or synthetic variant or a peptide fragment comprising at least 10 amino acids. Furthermore, the examiner alleges that the specification is not enabling for primers or oligonucleotides specific for PAP RNA or cDNA or for methods of increasing a PAP in a cell. Finally, the examiner alleges that the specification is not enabled for a method for increasing PAP-7 in a cell by introducing into said cell a PAP nucleic acid such that the nucleic acid is expressed and PAP-7 is produced in the cell.

Solely for the purpose of expediting prosecution, and without prejudice to the applicants' right to seek broader claims in a continuing application, the applicants have canceled claims 1-5, 34 and 35, thereby rendering moot the rejection as applied to each of those claims. New claim 41 is directed to (a) nucleic acids comprising the nucleotide acid sequence of SEQ ID NO: 2, (b) nucleic acids that encode the amino acid sequence of SEQ ID NO: 7, and (c) polynucleotides that are complementary to (a) or (b). The examiner

acknowledges that these sequences are enabled by the specification. [See Office Action, paragraph 6, page 4.] Claims ultimately dependent on claim 41, further limit the enabled polynucleotides to, e.g., vectors comprising such a polynucleotide, host cells comprising such vectors, processes producing polypeptides encoded by such polynucleotides, diagnostic reagents, and the like. The instant application enables one of skill in the art to make and use the enabled nucleic acids in such well known applications. Accordingly, each one of claims 10-16, and new claims 48-52, which ultimately depend from claim 41, is enabled.

The applicant also submits that new claims 42-47, and 53-76 should not be rejected pursuant to 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 42-44 are directed to nucleic acids that comprise a nucleic acid sequence that is at least 90% identical to the nucleic acids of claim 41 and encode a polypeptide that is capable of binding a peripheral-type benzodiazepine receptor (hereafter "PBR") or regulating steroid biosynthesis or mediating cholesterol delivery. The specification, at page 12, lines 3-31, page 40, lines 7-23 and Example 1, teaches how to identify polynucleotides that are at least 90% identical to the nucleic acids of claim 41 and that encode polypeptides that are capable of associating or binding with PBR using a yeast-based two-hybrid genetic assay (See pages 11 and 12). The yeast two-hybrid screening assay identified the gene sequence encoding the PBR associated protein 7 (PAP-7) (Example 1).

New claims 45-47 are directed to nucleic acids that comprise a nucleic acid sequence that hybridizes to the complement of SEQ ID NO: 2 under stringent conditions. The specification teaches one of skill in the art how to identify these variant polynucleotide sequences. Page 3, line 32 to page 4, line 8 and Example 3 provide methods to identify RNA from PAP related genes, which hybridize to a PAP-7 cDNA probe using Northern analysis. These methods provide guidance for identifying polynucleotides that hybridize under stringent conditions to the nucleic acid sequences of SEQ ID NO: 2. Further, the

specification defines these highly stringent hybridization conditions (page 17, lines 6-18), provides methods for carrying out the hybridization reactions (page 41, line 32 to page 42, line 8), and provides several references for one of skill in the art to refer to, *e.g.*, Sambrook, *et al.* and Ausubel, *et al.* (page 24, line 21 to page 25, line 11).

The variants recited in new claims 42-47 are also functionally defined in that the claimed variants are limited to those which are capable of binding a peripheral-type benzodiazepine receptor (PBR) or regulating steroid biosynthesis or mediating cholesterol delivery. The specification provides working examples that teach one of skill in the art how to screen for these functional requirements. In particular, Example 1 describes a method to identify a polypeptide (PAP or PBR associated protein) that binds PBR (see page 40, line 7 through 23; and page 44, line 27 to page 45, line 27.). Example 5 describes a method to identify a polypeptide that regulates steroid biosynthesis or mediates cholesterol delivery (page 42, lines 10-21; page 47, lines 14-26; and page 51, lines 11-33). Specifically, a fragment of PAP-7 acted as a competitor of native PAP-7 by binding to the PBR binding domain. The overexpressed PAP-7 fragment inhibited the normal function of PBR, thus inhibiting progesterone synthesis. Progesterone is an important precursor for all steroid hormones in steroid biochemical pathways. In addition, the applicants teach that PBR acts as a transporter of cholesterol, which is a precursor of progesterone (see page 51, lines 11-33). These results demonstrate that PAP-7 plays an important role in steroid biosynthesis through its interaction with PBR. In view of the structural and functional information about the claimed polynucleotides that is provided in the instant application, along with the instruction regarding how to use those polynucleotides, the applicants submit that the newly added claims 42-47 are supported by an enabling disclosure.

Claims ultimately dependent on claim 42-47 further limit the enabled polynucleotides to, *e.g.*, vectors comprising such a polynucleotide, host cells comprising such vectors,

processes producing polypeptides encoded by such polynucleotides, diagnostic reagents, and the like. The instant application enables one of skill in the art to make and use the enabled nucleic acids in such well known applications. Accordingly, each one of claims 53-76, which ultimately depend from either claim 42, 43, 44, 45, 46 or 47, is enabled

In view of the foregoing amendments and remarks, the applicants submit that the rejection of claims 1-5, 9-17, 34, and 35 pursuant to 35 U.S.C. § 112, first paragraph, for lack of enablement, has been overcome and should be withdrawn, and a rejection of new claims 41-76 on the same grounds would be improper.

Rejection Pursuant to 35 U.S.C. §112, first paragraph, written description–

The examiner asserted that claims 1-5, 9-17, 34, and 35 are rejected pursuant to 35 U.S.C. § 112, first paragraph, for failing to meet the written description requirement. Specifically, the examiner stated that claims directed to an isolated PBR-associated protein (PAP) DNA fragment or any portion thereof, an isolated and purified DNA fragment, which encodes a PBR-associated protein, DNA fragments of SEQ ID NO: 2 comprising at least 30 nucleotides, an isolated PAP-7 DNA fragment or natural or synthetic variant or a peptide fragment comprising at least 10 amino acids, an isolated DNA fragment which encodes a peptide of PBR-associated protein, and said DNA comprising a sequence specified in Genbank Accession Nos. AF022770 or AF020338 or a fragment of said sequence comprising at least 30 nucleotides are not described in the specification in such a way as to reasonable convey to one of skill in the art that the applicants were in possession of the claimed invention at the time of filing. [Office Action, paragraph 7.] In response, the applicants submit that these rejections have been rendered moot by the instant amendment.

Solely for the purpose of expediting prosecution, and without prejudice to the applicants' right to seen broader claims in a continuing application, the applicants have canceled claims 1-5, 34 and 35, thereby obviating the rejection to these claims. As discussed above, new claim 41 is directed to (a) nucleic acids comprising the nucleotide sequence of SEQ ID NO: 2, (b) nucleic acids that encode the amino acid sequence of SEQ ID NO: 7 and (c) nucleic acids that are complementary to (a) or (b). The examiner acknowledges that sequences (a) and (b) are fully described in the specification. [See Office Action, page 11, 12]. Applicants respectfully submit that nucleic acid sequences complementary to (a) or (b) are described in page 13, lines 14-17, page 17, lines 6-10, and Example 3.

New independent claims 42-47 are directed to variants of the PAP-7 protein that are at least 90% identical to SEQ ID NO: 2 and that exhibit the ability to bind the peripheral-type benzodiazepine receptor (PBR), regulate steroid biosynthesis, or mediate cholesterol delivery. These structural and functional characteristics of the subject matter of new claims 42-47 meet the Written Description Guidelines of the United States Patent Office (February, 2000). In particular, Example 14 of the guidelines teaches that a claimed variant polynucleotide that has a high percent identity to a sequence taught in the specification, along with a functional limitation that the claimed variant polynucleotides encode variant polypeptides that exhibit a specified catalytic activity, meet the written description if the required activity can be determined as described in the specification. In the instance claims, the claimed variants must each be at least 90% identical to SEQ ID NO: 2 (page 18, lines 15-27) and encode a polypeptide that retains the specified PBR binding activity, and/or retains the ability to regulate steroid biosynthesis, and/or retains the ability to mediate cholesterol delivery. These biological activities can be measured in assays as described in Examples 1 and 5. For example, the applicants disclose a polynucleotide encoding a fragment of SEQ ID NO: 2 with the PBR binding domain (page 51, lines 7-35). This fragment was able to retain the ability to

bind PBR and affectively regulate steroid biosynthesis by reducing the level of progesterone production in MA-10 cells (See Example 5, specifically page 51, lines 7-35). In addition to the variants of PAP, the claimed polynucleotides that hybridize under the high stringent hybridization conditions recited in claims 45-47 are explicitly supported in the specification at page 17, lines 6-18 and Example 3.

Accordingly, the structural and functional limitations of claims 42-47 are described in the specification in such a way as to convey to one of skill in the art that the applicants had possession of the claimed invention at the time of filing the application (see Examples 1, 3 and 5, page 17, lines 6-18, page 18, lines 15-27, and page 51, lines 3-35).

As similarly discussed above, claims ultimately dependent on claim 42-47 further limit the described polynucleotides to, *e.g.*, vectors comprising such a polynucleotide, host cells comprising such vectors, processes producing polypeptides encoded by such polynucleotides, diagnostic reagents, and the like. Thus, each one of the amended claims 10-16 and new claims 53-76, which ultimately depend from either claim 42, 43, 44, 45, 46 or 47, are fully described in the specification.

In view of the foregoing amendments and remarks, the applicants submit that the rejection of claims 1-5, 9-17, 34, and 35 pursuant to 35 U.S.C. § 112, first paragraph, for lack of written description, has been overcome and should be withdrawn, and a rejection of new claims 41-76 on the same grounds would be improper.

Rejection Pursuant to 35 U.S.C. §112, second paragraph, indefiniteness–

In paragraphs 9-12, the examiner rejected claims 1-5, 9-17, 34, and 35 pursuant to 35 U.S.C. § 112, second paragraph, as assertedly containing indefinite and vague terminology. In response, the applicants submit that the rejections have been rendered moot by amendment or cancellation to the relevant claims.

Solely for the purpose of expediting prosecution, and without prejudice to the applicants' right to seek broader claims in a continuing application, the applicants have spelled out all acronyms "PBR" and "PAP" in the claims for clarity as suggested by the examiner and for which the applicants are grateful. By canceling claims 34, support for the rejection based on the recitation of "and/or" has been rendered moot. Similarly, with regard to claim 35's alleged lack of a step indicating a PAP increase in a cell, cancellation of this has rendered moot the rejection. In view of the foregoing amendments and remarks, the applicants request the rejections pursuant to 35 U.S.C. § 112, second paragraph, has been overcome and should be withdrawn.

III. CONCLUSION

In view of the foregoing, the claims are still believed to be in form for allowance, and such action is hereby solicited. If any point remains in issue which the examiner feels may be best resolved through a personal or telephone interview, the examiner is **strongly urged** to contact the undersigned at the telephone number listed below.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By: _____

Thomas A. Cawley, Jr., Ph.D.
Registration No.: 40,944
Direct Telephone No.: 703-905-2144
Direct Facsimile No.: 703-738-2123

TAC/
P.O. Box 10500
McLean, VA 22102
General Telephone: 703-905-2000
General Facsimile: 703-905-2500